Pharmaceutical Processing with Supercritical Carbon Dioxide

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Abstract ☐ Replacement of traditional solvents with "environmentally benign" carbon dioxide is receiving increased attention in pharmaceutical processing. Among the reported applications, particle formation with dense carbon dioxide and the "clean" synthesis of drug compounds using carbon dioxide as a reaction medium hold immense potential for large-scale application in the pharmaceutical industry. This paper provides an overview of these rapidly emerging technologies along with examples of the wide variety of relatively contaminant-free pharmaceutical compounds that have been processed via these technologies on a laboratory scale. Challenges facing successful implementation in practice include demonstration of continuous production *and* harvesting of particles with desired and reproducible product characteristics. Mathematical models aimed at a better fundamental understanding of the underlying thermophysical phenomena are essential for rational design and scale-up of these technologies.

Introduction

Conventional pharmaceutical processing involves extensive use of organic solvents as either antisolvents for recrystallizing drugs from solutions, reaction media in the synthesis of drugs, or extracting agents for selectively isolating drugs from solid matrices. Health concerns caused by some of these solvents such as methylene chloride by way of either environmental emissions and/or trace residues in the product have propelled research efforts aimed at developing "environmentally benign" processing techniques that either eliminate or significantly mitigate pollution at the source. A major research focus in this regard has been the investigation of processes in which the traditional solvents are replaced with supercritical carbon dioxide. Among the reported applications, the formation of drug particles using dense carbon dioxide either as a solvent or nonsolvent and the "clean" synthesis of drug compounds using carbon dioxide as a reaction medium hold immense appeal for large-scale application in the pharmaceutical industry. This paper provides a perspective of recent progress in these areas addressing some of the research and scale-up challenges facing successful implementation of these promising technologies in practice. The applications of supercritical carbon dioxide in preparative or analytical chromatography of drug compounds and for extraction of pharmaceutical compounds have been reviewed elsewhere[1-4] and hence are not covered in this review.

Carbon Dioxide Properties

A substance is termed supercritical when its pressure and temperature are greater than its critical pressure (P_c) and critical temperature (T_c), respectively. Along a near-critical isotherm (between T_c and $1.2T_c$), the density, transport properties (such as viscosity and diffusivity), and other physical properties (such as dielectric constant and solvent strength) can be varied in a continuum from gas-like to liquid-like with relatively small changes around the critical pressure ($0.9-2.0P_c$). Thus, it is possible to realize unique fluid properties to suit various processing needs. The properties and various applications of supercritical fluids are summarized elsewhere.[4]

For pharmaceutical applications, carbon dioxide is an ideal processing medium. Because of its relatively mild critical temperature (31.1 °C), it is possible to exploit the advantages of near-critical operation at temperatures lower than 35 °C. Furthermore, carbon dioxide is nontoxic, nonflammable, relatively inexpensive (quoted between $0.05 and 0.07 per lb), recyclable, and "generally regarded as safe". Even though the critical pressure (73.8 bar) of carbon dioxide is relatively high, such operating pressures and operating equipment thereof are fairly routine in large-scale separation processes involving supercritical carbon dioxide such as the decaffeination of coffee beans and the extraction of hops.[4]

Carbon dioxide is a nonpolar solvent. A common rule of thumb is that if a compound dissolves in hexane, then that compound should also dissolve in supercritical carbon dioxide. While this rule is valid for many low molar mass compounds that have appreciable vapor pressures, it fails in the case of polymers which have negligible vapor pressures. As such, carbon dioxide is essentially a nonsolvent for many lipophilic and hydrophilic compounds (which covers most pharmaceutical compounds). Supercritical carbon dioxide has been exploited both as a solvent and as a nonsolvent or antisolvent in pharmaceutical applications. The ability to rapidly vary the solvent strength, and thereby the rate of supersaturation and nucleation of dissolved compounds, is a unique aspect of supercritical technology for particle formation.

Particle Formation Using Compressed Carbon Dioxide

Conventional techniques for particle size reduction include mechanical comminution (crushing, grinding, and milling), recrystallization of the solute particles from solution using liquid antisolvents, freeze-drying, and spray-drying. Among the limitations associated with these processes are excessive solvent use and disposal, thermal and chemical degradation of products, trace residues, and interbatch particle size variability. Therefore, the production of contaminant-free microparticles with controlled particle size and desired product qualities in an environmentally responsible manner continues to be a major challenge. The subject of particle formation with supercritical fluids has been reviewed previously.[5-8] This paper complements these reviews by emphasizing recent developments.

Recrystallization using Carbon Dioxide as a Solvent—In this process, the solute is first solubilized in the supercritical fluid. The solution is then expanded across a nozzle or capillary at supersonic velocities. The rapid expansion leads to supersaturation of the solute and subsequent precipitation of virtually contaminant-free particles. This process of particle formation has been termed supercritical

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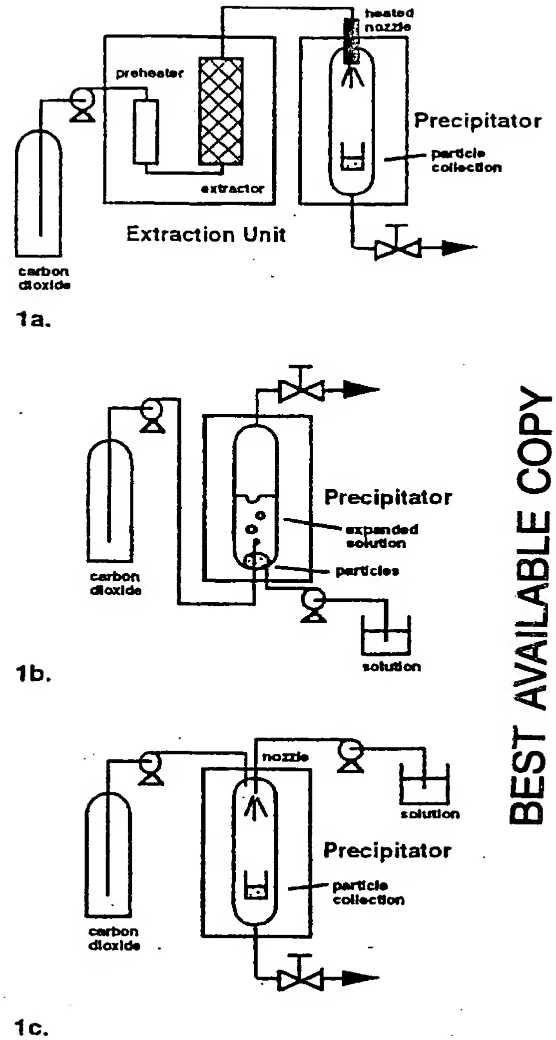

Figure 1—Schematics of the (a) RESS, (b) GAS, and (c) PCA/SAS/ASES processes.

fluid nucleation[9] and rapid expansion of supercritical solutions (RESS).[10] A process schematic is shown in Figure 1a. The RESS process has been demonstrated to produce contaminant-free drug microparticles ranging from a few microns to several hundred microns. Table 1 summarizes some of the reported studies.[11–22] The RESS process has also been applied for coprecipitation of solutes such that one of the solutes is coated on the other.[23]

The factors that affect particle size and morphology in the RESS process include the length/diameter ratio of the expansion device,[17] the RESS time-scale dictated by the expansion trajectory from the preheater and the expansion device,[24] and particle agglomeration during free jet expansion. If the precipitation density occurs in the preheater, the expansion occurs over tens of seconds and fibers result. On the other hand, if the precipitation density occurs in the expansion device, the RESS process occurs in the order of microseconds and relatively small particles result. Various mathematical models have been proposed to predict particle size during subsonic expansion,[25,26] to correlate particle size/morphology based on a one-dimensional solvent expansion,[17,24,27] and to describe the fluid dynamics of free jet expansion.[28] A comprehensive model that accounts for expansion in the nozzle and in the jet along with nucleation, growth, and agglomeration remains a challenge.

A major limitation of the RESS process is that, at moderate temperatures and pressures (<60 °C and 300 bar), the solubilities of pharmaceutical compounds in supercritical carbon dioxide are on the order of 0.01 wt % or less (see Table 1). Hence, relatively large amounts of carbon dioxide are required for increased product throughput. Cosolvents, such as methanol, may be added to carbon dioxide to enhance solubilities. However, these added solvents affect the otherwise environmentally benign nature of the RESS process. Other challenges are the operational and scale-up issues associated with nozzle design in order to avoid particle accumulation and freezing caused by the rapid expansion.

Recrystallization Using Carbon Dioxide as a Nonsolvent or Antisolvent—The relatively low solubilities of pharmaceutical compounds in unmodified carbon dioxide are exploited in this process wherein the solute of interest (typically a drug, polymer or both) is dissolved in a conventional solvent to form a solution. The preferred ternary phase behavior is such that the solute is virtually insoluble in dense carbon dioxide while the solvent is completely miscible with dense carbon dioxide at the recrystallization temperature and pressure. The solute is recrystallized from solution in one of two ways. In the first method, a batch of the solution is expanded several-fold by mixing with dense carbon dioxide in a vessel (Figure 1b). Because the carbon dioxide-expanded solvent has a lower solvent strength than the pure solvent the mixture becomes supersaturated, forcing the solute to precipitate or crystallize as microparticles. This process was termed gas antisolvent (GAS) recrystallization.[29] The second method involves spraying the solution through a nozzle as fine droplets into compressed carbon dioxide (Figure 1c). This process has been termed in general as precipitation with compressed antisolvents (PCA)[30] and employs either liquid or supercritical carbon dioxide as the antisolvent. When using a supercritical antisolvent, the spray process has been termed supercritical antisolvent (SAS) process[31] or aerosol spray extraction system (ASES).[32]

The GAS or PCA process is thus complementary to RESS. Advantages include higher solute throughput and the flexibility of solvent choice. As summarized in Table 2[8,33–43] the PCA/SAS/ASES and GAS techniques have been used to micronize a wide variety of pharmaceutical compounds such as polymers used in controlled-release formulations (Figure 2a), protein powders (Figure 2b), and anti-inflammatory agents (Figure 2c). The reported particle sizes range from submicron to a few microns in a narrow size range. These size ranges encompass those suitable for either pulmonary delivery (1−3 μm) or use in implantable devices (<100 μm). It is noteworthy that, in the case of insulin, the biologic activity and structure upon reconstitution in water are preserved.[43] The spray process has also been demonstrated to produce drug-loaded polymeric microspheres such as drug/PLGA[38] and drug/HYAFF-11.[41] In addition to particle formation, the GAS process has also been used for separation of solutes from solution by exploiting the different dependence of the solubilities upon expansion of the solution.[20,44]

Standard capillary nozzles, ultrasonic atomizers, and coaxial nozzles have been employed to spray the solution. Using either a capillary (75 μm i.d.) or an ultrasonic spray nozzle Randolph *et al.*[34] reported submicron L-PLA microspheres of similar sizes when spraying 0.6 wt % PLA/methylene chloride solution into supercritical carbon dioxide. This led them to speculate that interphase mass transfer rates rather than initial droplet size control eventual particle size. Using 10 μm capillary nozzles, Bodmeier *et al.*[35] reported that a higher L-PLA concentration (>4 wt %) led to fiber formation instead of microspheres. Besides requiring less antisolvent to precipitate the polymer, the increased viscosity at higher polym

Table 1—Solubilities and RESS Studies of Pharmaceutical Compounds in Carbon Dioxide

Solute	Cosolvent	Solubility[a]	T (°C)	P (bar)	Particle Mean Diameter (μm)	Ref
Mevinolin (Lovastatin)	—	4ω	40	345		11
	5% MeOH[c]	10–45ω	40	103–379	10–50 (3% MeOH)	11
Efrotomycin	—	3ω	40	345		11
Imipenem	—	0ω	40	345		11
Mevinolin (Lovastatin)	—	0.09–3.4ω	55	125–409	0.1–0.3[i] (379 bar) 0.04–0.07[j]	12
	—	0.1–6ω	75	134–409		12
Digoxin	—	0.18y	50	241	b	13
	7.2 mol % MeOH	0.17y	50	241	b	13
Griseofulvin	—	1.5y	50	241	b	13
	3.5 mol % CH_2Cl_2	1.4y	50	241	b	13
	3.4 mol % Butyl acetate	6.4y	50	241	b	13
Aspirin	—	0.12–26y	45	60–228	b	14
Salicylic acid	—	14y	45	138–241	b	14
	Benzoic acid (trace)	14y	45	102–238	b	14
Stigmasterol	—		100	100	0.05–0.2 amorphous	15
	—		100	150	0.2, 2–3 length whiskers	15
L-PLA[d] (MW 5500; extracted MW 1000–2000)	—	1.3–4.3ω	45	200–300	b	16
	—	2.4–5.3ω	55	200–300	4–10 (250 bar)	16
	—	2.8–7.4ω	65	200–300	b	16
	1% (w/w) Acetone	5.5–16ω	45	200–300	b	16
	1% (w/w) Acetone	13–25ω	55	200–300	10–25 (200–230 bar)	16
	1% (w/w) Acetone	21–37ω	65	200–300	b	16
DL-PLA[e] (MW 5300)	—	—	55	200	10–20	16
PGA[f] (MW 6000)	—	—	55	180–200	10–20	16
L-PLA (MW 10,000)	40% (w/w) $CHClF_2$[g]	0.18–7.7ω	65	72–200	b	17
	19–58% (w/w) $CHClF_2$		55	~200	2–5[k]	17
	30% (w/w) $CHClF_2$		55	~200	<50[l]	17
Testosterone	—	0.23–5.0y	35	88–242	b	18
	—	0.04–7.0y	55	87–242	b	18
Progesterone	—	0.99–5.9y	35	105–244	b	18
	—	0.11–7.4y	55	109–243	b	18
Cholesterol	—	0.61–28y	55	102–276	b	18
Salicylic acid	—	10–53y	40	100–350	b	19
	—	8.3–67y	60	115–325	2–20 (200 bar)	19
Ketoprofen	—	1.3–8.0y	39.4	100–220	b	20
	—	0.78–15y	58.4	116–220	b	20
Piroxicam	—	0.45–4.3y	39.4	100–220	b	20
	—	0.37–3.9y	58.4	130–220	b	20
Nimesulide	—	1.9–7.4y	39.4	130–220	b	20
	—	0.85–9.8y	58.4	130–220	b	20
Salicylic acid	—	—	43	223	<4	21
Theophylline	—	—	65	225	0.4	21
PEG[h] (MW 4000)	—	—	60–70	100–200	170–370	22

[a] ω, mass fraction (10^4); y, mole fraction (10^5). [b] Solubility study only. [c] Methanol. [d] Poly(L-lactic acid). [e] Poly(D,L-lactic acid). [f] Poly(glycolic acid). [g] T_c = 369.3 K, = 49.7 bar. [h] Polyethylene glycol. [i] After sonication. [j] Standard deviation. [k] Entrance length of capillary L/D = 500. [l] Entrance length of capillary L/D = 167.

concentrations tends to stabilize the jet, leading to rapid skin formation. Saim *et al.*[39] observed similar trends when spraying hyaluronic acid ester (HYAFF-7)/DMSO solution into supercritical carbon dioxide. Bertucco *et al.*[41] used the GAS process, instead of the spray process, to obtain submicron microspheres of HYAFF-11. In the GAS process, mixing and the rate at which the solution is expanded determine nucleation rates and eventual particle size. Recently, York and Hanna[42] reported the use of coaxial spray nozzles to separately introduce the solution and antisolvent, obtaining particles of salmeterol xinafoate in the 1–10 μm range.

The studies referenced in Table 2 clearly demonstrate that techniques using carbon dioxide as a nonsolvent can produce drug particles in a narrow size distribution using fewer organic solvents. Because the spray-processes (PCA, SAS and ASES) permit faster depletion of the solvent (and hence greater production rate of particles) relative to the GA process, they have received increased attention in recei years. However, invariably all reported studies are of tl proof-of-concept type, dealing with batch production of mi ligram quantities of product at most. For the spray process to be commercially viable, continuous production of particl with desired product characteristics and consistency has be demonstrated. In particular, continuous harvesting particles at high yield remains a challenge, especially wi submicron particles.

In the spray process, the particle size and morphology a dependent on several factors such as the operating pressur temperature, jet breakup, and the mass transfer rates b tween the droplet and antisolvent phases. Jet breakup ar the droplet sizes depend on the relative magnitudes of tl droplet deforming (inertial, external) and reforming (viscou

Table 2—GAS/SAS/PCA Studies of Pharmaceutical Compounds in Dense Carbon Dioxide

Solute	Solution	Process	Solution, CO_2 Flow Rate	T (°C)	P (bar)	Nozzle Diam (μm)/ Particle Diam (μm)	Re
Insulin	5 and 15 mg/mL in DMSO,[a] 5 mg/mL in DMF	SAS	0.3 mL/min, 8.0 SLPM	25, 35	86.2	30/2–4	33
	5 mg/mL in DMSO	GAS		35	0.57 bar/min to 86.2 bar	4	33
L-PLA[b] (MW 100 000)	0.6% (w/w) in CH_2Cl_2	PCA batch	1 mL/min, stagnant	31	76–97	75/0.6–1.4 (0.5)[j]	34
	0.3% (w/w) in CH_2Cl_2	PCA	1 mL/min, 5.34 SCFM	36	76–83	Ultrasonic/0.8–2.8 (0.3)	34
L-PLA (MW 94 100)	3% (w/v) in CH_2Cl_2	PCA	—	0	81.6	100/<1	35
	3% (w/v) in CH_2Cl_2	PCA	—	23, 32	81.6	100/1–5	35
(+)-Chlorpheniramine maleate (10%/3.7%)[c]	4% (w/v) in CH_2Cl_2	PCA	—	22	69	100/1–5	35
(+)-Indomethacin (10%/0.7%)[c]	4% (w/v) in CH_2Cl_2	PCA	—	22	69	100/1–5	35
L-PLA (MW 102 000) (+)-Hycosine-butylbromide (20%/19.5, 19.8%)[c]	2% (w/w) in CH_2Cl_2	PCA batch	6 mL/min, stagnant	40	90, 200	400/13.2[k] (23.1)[l], 14.9[k] (26.4)	36
(+)-Indomethacin (20%/0.5%)[c]	2% (w/w) in CH_2Cl_2	PCA	6 mL/min, 6 kg/h	40	200	400/8.2[k] (15.3)	36
(+)-Piroxicam (20%/6.8, 3.7%)[c]	2% (w/w) in CH_2Cl_2	PCA	6 mL/min, 6 kg/h	40	90, 200	400/3.5[k] (6.0), 2.8[k] (3.7)	36
(+)-Thymopentine (5%/4.8, 4.9%)[c]	2% (w/w) in CH_2Cl_2/MeOH	PCA	6 mL/min, 6 kg/h	40	90, 200	400/6.6[k] (12.1), 5.1[k] (8.7)	36
L-PLA (MW 115 000 + MW 7000)	3% (w/w) in CH_2Cl_2	PCA	—	30–45	85	300/7[k] (9)[l] 26[k] (36)	37
	3% (w/w) in CH_2Cl_2	PCA	—	40	65–125	300/50[k] (55) –10[k] (20)	37
PLGA[d] + TP5[e]	5% and 10% TP5, 1% and 5% lecithin 27 mL of CH_2Cl_2, 2 mL of MeOH, 3 mL of acetic acid, 15 mL of hexafluoroisopropanol	PCA	5.5 mL/min, 9.7 kg/h	35	85	300/60[k] (5% TP5), 40[k] (10% TP5)	38
HYAFF-7[f]	200–500 ppm in DMSO	PCA	2.5 mL/min, 5 mL/min	40	104	100/50–500	39
PLGA[d]	0.5 mg/mL in DMSO	PCA	2.5 mL/min, 5 mL/min	35	104	100/15	39
Hydrocortisone	200–500 ppm in DMSO	PCA	2.5 mL/min, 5 mL/min	35	104	100/0.2–1	39
MRA[g]	10% (w/w) in THF[i]	PCA	2.7 mL/min, ~40 g/min	-6–63	151	510/2.5–3.2	40
Hydrocortisone acetate	Dimethyl formamide	PCA	2.9 and 1.8 mL/min, 70 and 79 g/min	45, 65	150	510/8.4, 7.8	40
HYAFF-11[f] + protein	1% (w/w) in DMSO	GAS	CO_2 bubbled through solution	40, 35	15, 20 bar/min to 100 bar	0.36–0.40, 0.32–0.34 (~0.15)[m]	41
Salmeterol xinafoate	0.5% (w/v) in Acetone	PCA	0.1–0.3 mL/min, 8 mL/min	35	100	—/10–16	42
	0.5% (w/v) in Acetone	PCA	0.1–0.3 mL/min, 8 mL/min	35	200	—/9–12	42
	0.5% (w/v) in Acetone	PCA	0.1–0.3 mL/min, 8 mL/min	35	300	—/4–7	42
Insulin	0.5–9.2 mg/mL in DMSO	SAS	0.9–1.7 mL/min, 9–26 SLPM	28–46	91–142	30 or 50/1–5[k]	43
Lysozyme	2.2–6.8 mg/mL in DMSO	SAS	0.2–2.4 mL/min, 10–21 SLPM	27–45	73–115	30 or 50/1–5[k]	43
Trypsin	0.1–4.0 mg/mL in DMSO	SAS	0.5–2.1 mL/min, 5–20 SLPM	27–47	73–136	30 or 50/1–5[k]	43
DL-PLA[h] (MW 5000)	36 mg/mL in DMSO	SAS	0.25 mL/min, 15 SLPM	36	104	—, < 2 μm	8

[a] Dimethyl sulfoxide. [b] Poly(l-lactic acid). [c] (Expected drug loading/actual drug loading): the amount of drug in the precipitate (actual) was less than the amount o drug mixed with the polymer prior to precipitation (expected), due to partitioning of the drug into CO_2 during microparticle formation; *e.g.*, (20%/6.8, 3.7%) means 6.8% drug loading at 90 bar, 3.7% drug loading at 200 bar. [d] Poly(dl-lactide-glycolide). [e] Thymopentine. [f] Hyaluronic acid ethyl ester. [g] Methylprednisolone acetate. [h] Poly(DL lactic acid). [i] Tetrahydrofuran. [j] Relative standard deviation. [k] After sonication. [l] Range: 10th–90th percentile. [m] Standard deviation.

interfacial tension) forces. These forces in turn are dictated by the nozzle configuration, the spray velocity, and the physical properties of the droplet and antisolvent phases. The mass transfer between the droplet and antisolvent phases occurs between the two limiting pathways, *viz.*, solvent evaporation with little carbon dioxide penetration into the droplet phase, and carbon dioxide swelling of the droplet phase with no solvent evaporation. In the case of polymers, various morphologies result, depending on where the mass transfer trajectory crosses the coexistence region of the ternary phase diagram.[30] While some useful attempts have been made to interpret the effects of process variables on particle size and morphology in terms of the dimensionless groups (Reynolds, Weber, and Ohnesorge groups) that characterize the spray dynamics and jet breakup,[30,39,45] a rigorous mathematical model of the spray process based on the underlying rate processes (spray dynamics, mass transfer, and nucleation processes) is needed for a better mechanistic understanding. Such an understanding is essential to rational design and scale-up.

Clean Chemistry with Supercritical Carbon Dioxide

The use of supercritical carbon dioxide as a nonaqueous solvent medium for enzymatic reactions has been known for more than a decade.[46,47] When compared to conventional organic solvents, supercritical carbon dioxide offers several advantages. The higher diffusivities, lower viscosities, and lower surface tension result in enhanced reaction rates. The tunability of the density and transport properties of the supercritical fluid not only allows the manipulation of the reactions but also aids in product separation. Furthermore the water solubility of supercritical carbon dioxide at 40 °C and 150 bars is about 2 orders of magnitude greater than in hexane. This greater water solubility helps stabilize the structure of the enzyme against conformational changes that lead to deactivation.[48] Among the reported applications, the kinetic resolution of enantiomers by lipase-catalyzed reactions in supercritical carbon dioxide shows commercial promise.[49]

Supercritical carbon dioxide has also been shown to be an environmentally sound reaction medium for synthesizing a

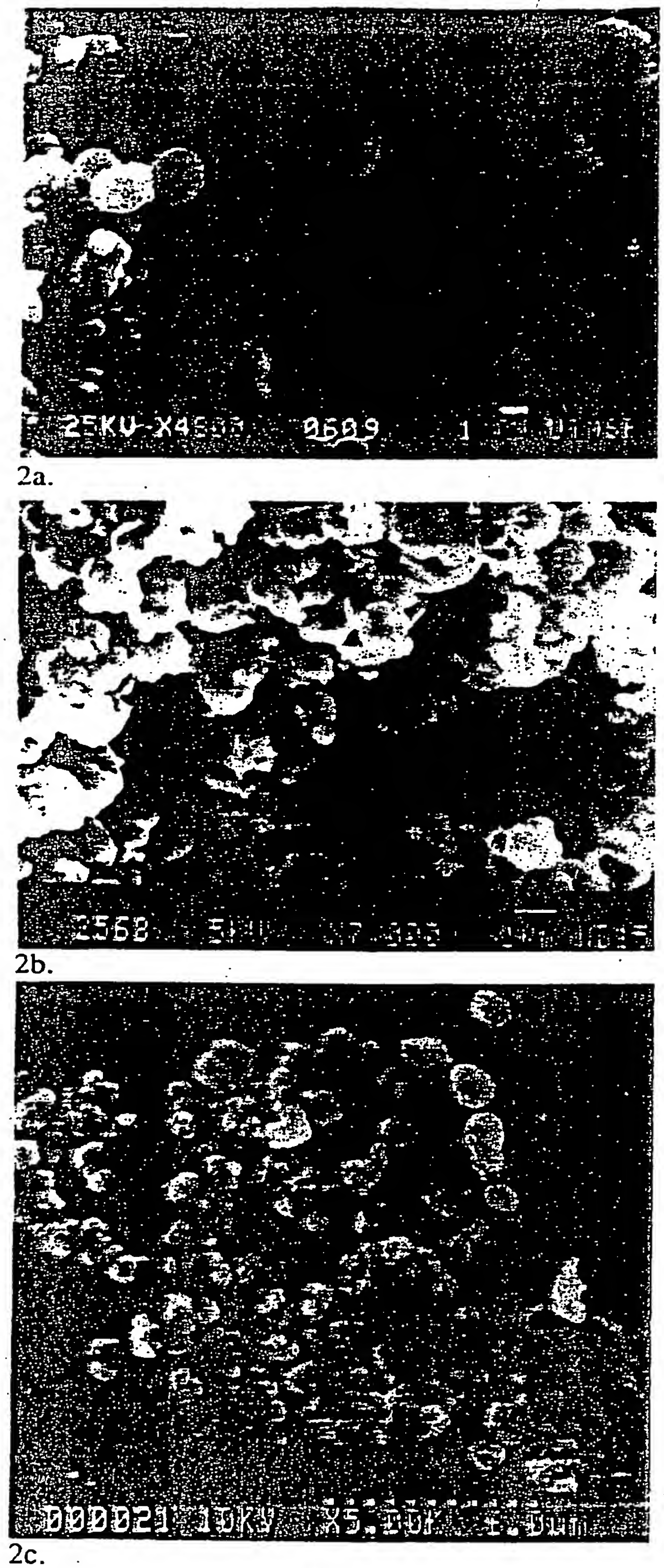

Figure 2—Micronization of (a) L-PLA,[35] (b) lysozyme,[43] and (c) hydrocortisone,[39] using carbon dioxide as an antisolvent. Processing conditions are given in Table 2. (This figure is reprinted: (a) From ref 35. Copyright 1995 Plenum. (b) From ref 43. Copyright 1996 ACS and APhA. (c) From ref 39. Copyright 1996 Plenum.)

wide range of polymers.[50] In particular, dispersion polymer ization in supercritical carbon dioxide provides a chemica route for formation of discrete polymer particles with con trolled size and morphology.[51] The key to this process is th synthesis of polymer surfactants that contain a lipophili backbone that acts as an anchor for a fluorinated branch chai that is CO_2-philic. The lipophilic backbone adsorbs to th growing particle of the polymer synthesized (*e.g.* PMMA) an the fluorocarbon extends into the carbon dioxide phase. Usin poly (FOA) as a stabilizer (surfactant polymer) and F-AIB as a carbon dioxide-soluble initiator, uniform dispersions o PMMA polymer particles (1–3 μm) of high molar mass an high yield were obtained in supercritical carbon dioxide. Thi process offers a potentially attractive strategy for synthesi of controlled-size polymers for use in controlled-release for mulations.

The use of supercritical carbon dioxide as an alternative t aqueous and organic solvents requires the addition of suitabl surfactants, since many nonvolatile, hydrophilic compound (such as proteins, catalysts, and other pharmaceutical com pounds) are poorly soluble in CO_2. Perfluoropolyether (PFPE has been shown to form microemulsions of water in CO_2.[5] Bovine serum albumin (BSA) was soluble in these microemul sions and retained its biological activity after recovery. Graf and block copolymers composed of a CO_2-philic perfluorocar bon component and a CO_2-phobic component have bee demonstrated to form micelles in supercritical CO_2.[53,54] Th core of the micelle contained either water or hydrocarbo oligomers, depending on the nature of the CO_2-phobic com ponent. These examples open new avenues for exploitin supercritical carbon dioxide in reaction and particle formatio processes.

Concluding Remarks

Supercritical carbon dioxide offers several attractive tech nological scenarios for pharmaceutical processing that coul result in significantly reduced usage of conventional liqui solvents and the production of relatively contaminant-fre products. Among the several applications reported in th literature, particle micronization with supercritical carbo dioxide offers a unique technology for producing micron an submicron particles with controlled particle size and purity Challenges facing successful implementation of the technolog include scale-up, demonstrating continuous production c particles with desired, and reproducible product quality. A fundamental understanding of the underlying thermophysica processes is essential for rational scale-up and design.

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